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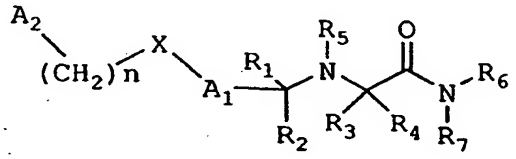
(54) Title: SUBSTITUTED 2-AMINOACETAMIDES AND THE USE THEREOF



(II)

(57) Abstract

This invention is related to substituted 2-aminoacetamides represented by formula (II): or a pharmaceutically acceptable salt or prodrug thereof, wherein the substituents are defined herein. The invention also is directed to the use of substituted 2-aminoacetamides for the treatment of neuronal damage following global and focal ischemia, for the treatment or prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), and for the treatment, prevention or amelioration of pain, as anticonvulsants, and as antimanic depressants, as local anesthetics, as antiarrhythmics and for the treatment or prevention of diabetic neuropathy.

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Substituted 2-Aminoacetamides and the Use Thereof

Background of the Invention

Field of the Invention

This invention is in the field of medicinal chemistry. In particular, the invention relates to substituted 2-aminoacetamides and the discovery that these compounds act as blockers of sodium (Na^+) channels.

Related Background Art

Several classes of therapeutically useful drugs, including local anesthetics such as lidocaine and bupivacaine, antiarrhythmics such as propafenone and amioclarone, and anticonvulsants such as lamotrigine, phenytoin and carbamazepine, have been shown to share a common mechanism of action by blocking or modulating Na^+ channel activity (Catterall, W.A., *Trends Pharmacol. Sci. 8*:57-65 (1987)). Each of these agents is believed to act by interfering with the rapid influx of Na^+ ions.

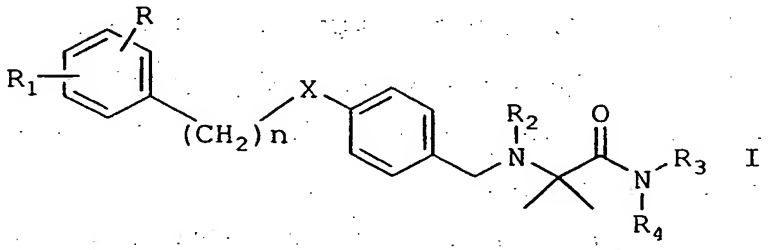
Recently, other Na^+ channel blockers such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia and are presently in clinical trials (Graham *et al., J. Pharmacol. Exp. Ther.* 269:854-859 (1994); Brown *et al., British J. Pharmacol. 115*:1425-1432 (1995); *SCRIP 1870*:8 (1993); *SCRIP 1773*:14 (1992)).

The neuroprotective activity of Na^+ channel blockers is due to their effectiveness in decreasing extracellular glutamate concentration during ischemia by inhibiting the release of this excitotoxic amino acid neurotransmitter. Studies have shown that unlike glutamate receptor antagonists, Na^+ channel blockers prevent hypoxic damage to mammalian white matter (Stys *et al., J. Neurosci. 12*:430-439 (1992)). Thus, they may offer advantages for treating certain types of strokes or neuronal trauma where damage to white matter tracts is prominent.

Another example of clinical use of a Na^+ channel blocker is riluzole. This drug has been shown to prolong survival in a subset of patients with ALS (Bensimm *et al., New Engl. J. Med. 330*:585-591 (1994)) and has subsequently been approved by the FDA for the treatment of ALS. In addition to the above-mentioned clinical uses, carbamazepine, lidocaine and phenytoin are occasionally used to treat neuropathic pain, such as from trigeminal neurologia, diabetic neuropathy and other forms of nerve damage (Taylor and Meldrum, *Trends Pharmacol. Sci. 16*:309-316 (1995)), and carbamazepine and lamotrigine have been used for the treatment of manic depression (Denicott *et al., J. Clin. Psychiatry 55*: 70-76 (1994)).

It has been established that there are at least five to six sites on the voltage-sensitive Na^+ channels which bind neurotoxins specifically (Catterall, W.A., *Science 242*:50-61 (1988)). Studies have further revealed that therapeutic antiarrhythmics, anticonvulsants and local anesthetics whose actions are mediated by Na^+ channels, exert their action by interacting with the intracellular side of the Na^+ channel and allosterically inhibiting interaction with neurotoxin receptor site 2 (Catterall, W.A., *Ann. Rev. Pharmacol. Toxicol. 10*:15-43 (1980)).

PCT International Published Application WO 90/14334 and WO 97/05102 disclose 2-(4-substituted)-benzylamino-2-methyl-propanamide derivatives represented by Formula **I**:



I

where n is 0-3; X is O, S, CH_2 or NH; each of R and R_1 independently is hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-4} alkoxy, or trifluoromethyl; each of R_2, R_3 and R_4 independently is hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl. The

compounds are disclosed to be useful as antiepileptics, in the treatment of Parkinson's disease and as neuroprotective agents, e.g. preventing or treating neuronal loss associated with stroke, hypoxia, ischemia, CNS trauma, hypoglycemia or surgery, and in treating and preventing neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Down's syndrome, Huntington's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia and infections or inflammations in the brain; they can also be used as antidepressants, hypnotics, and antispastic agents and in treating ocular damage and retinopathy. However, their mechanism of action was not disclosed.

Summary of the Invention

The present invention is related to treating a disorder responsive to the blockade of sodium channels in a mammal suffering from excess activity of said channels by administering an effective amount of a compound of Formula **I**. The present invention is also related to treating a disorder responsive to the blockade of sodium channels in a mammal suffering therefrom by administering an effective amount of a compound of Formula **II** as described herein.

The present invention is also directed to the use of a compound of Formulae **I** or **II** for the treatment of neuronal damage following global and focal ischemia, and for the treatment or prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), as antimanic depressants, as local anesthetics, as antiarrhythmics and for the treatment or prevention of diabetic neuropathy and for the treatment of pain including chronic pain.

The present invention also is directed to the process for preparing novel substituted 2-aminoacetamide of Formula **II**.

A first aspect of the present invention is directed to the use of compounds of Formulae **I** or **II** as blockers of sodium channels.

A second aspect of the present invention is to provide a method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating pain including chronic pain; treating, preventing or ameliorating neurodegenerative conditions; treating, preventing or ameliorating manic depression; inducing local anesthesia; and treating arrhythmias by administering a compound of Formulae **I** or **II** to a mammal in need of such treatment.

A number of compounds within the scope of the present invention are novel compounds. Therefore, a third aspect of the present invention is to provide novel compounds of Formula **II**, and to also provide for the use of these novel compounds for treating, preventing or ameliorating convulsions.

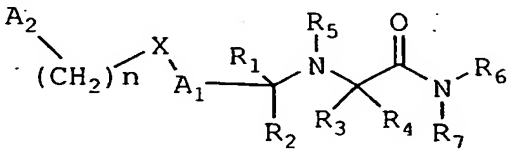
A fourth aspect of the present invention is to provide a pharmaceutical composition useful for treating disorders responsive to the blockade of sodium ion channels, containing an effective amount of a compound of Formulae **I** or **II** in a mixture with one or more pharmaceutically acceptable carriers or diluents.

A fifth aspect of the present invention is directed to methods for preparing novel compounds of Formulae **II**.

Detailed Description of the Invention

The present invention arises out of the discovery that compounds of Formulae **I** and **II** act as blocker of the Na^+ channel. In view of this discovery, compounds of Formulae **I** and **II** are useful for treating disorders responsive to the blockade of sodium ion channels.

The compounds useful in this aspect of the present invention are substituted 2-aminoacetamides represented by Formula **II**:



II

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1 R_2, R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R_5, R_6 and R_7 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R_5, is defined as above, and R_6 and R_7 together with the nitrogen atom to which they are attached form a heterocycle;

A_1 and A_2 are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR_8, CH_2, C(O), $NR_8C(O)$, $C(O)NR_8$, SO, SO_2 or a covalent bond; where

R_8 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

n is 0, 1, 2 or 3.

Preferred compounds falling within the scope of Formula **II** include compounds wherein A_1 and A_2 are both aryl moieties, preferably both phenyl moieties, that are each optionally independently substituted by one or two substituents independently selected from the group consisting of halogen, nitro, amino, C_{1-6} alkyl, C_{3-8} cycloalkyl, cyano, C_{1-6} alkoxy or C_{6-10} aryloxy; R_1 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or C_{6-10} aryl; O or S.

Preferred compounds within Formula **II** also include those compounds where A_1 is an optionally substituted aryl group selected from the group consisting of phenyl and naphthyl, and A_2 is an optionally substituted heteroaryl or aryl group selected from the group consisting of pyridyl, pyrimidinyl, 1,3,5-triazinyl, furanyl, thiophenyl, naphthyl, quinolyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, indanyl, tetrahydronaphthyl, biphenylmethyl, triphenylmethyl and quinoxalinyl.

Additional preferred compounds within Formula **II** also include those compounds where A_1 is an optionally substituted aryl group selected from the

group consisting of phenyl or naphthyl, and A_2 is an optionally substituted carbocycle or heterocycle selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, cyclohexenyl, adamantyl, *exo*-norbornyl and cyclopentenyl.

Additional preferred compounds within Formula **II** include those compounds where A_1 is an optionally substituted heteroaryl or aryl group selected from the group consisting of pyridyl, pyrimidinyl, 1,3,5-triazinyl, naphthyl, quinolyl, furanyl, and thiophenyl, and A_2 is an optionally substituted heteroaryl or aryl group selected from the group consisting of phenyl, furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, indanyl, tetrahydronaphthyl and naphthyl.

Additional preferred compounds within Formula **II** include those compounds where A_1 is an optionally substituted, saturated or partially unsaturated carbocycle or heterocycle selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, morpholinyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl and tetrahydropyranyl, and A_2 is an optionally substituted aryl or heteroaryl group selected from the group consisting of phenyl, furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, indanyl, tetrahydronaphthyl, or naphthyl.

Exemplary preferred compounds that may be employed in this method of invention include, without limitation:

2-(4-(2-fluorobenzyloxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxyphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxybenzyloxy)benzylamino)-2-methyl-propanamide;

2-(4-cyclohexyloxybenzylamino)-2-methyl-propanamide;

2-(4-(5,6,7,8-tetrahydro-2-naphthoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-adamantanoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-Chloro-2-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-bromo-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-nitrophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-tetrahydropyranoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,5-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-chlorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-methylphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-chloro-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(5-indanoxy)benzylamino)-2-methyl-propanamide;

2-(4-cycloheptoxybenzylamino)-2-methyl-propanamide;

2-(4-(1-methyl-4-piperidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(exo-2-norbornoxy)benzylamino)-2-methyl-propanamide;

2-(3-(4-fluorophenoxy)-5-pyridylmethylamino)-2-methyl-propanamide;

2-(4-(4-pyridinoxy)benzylamino)-2-methyl-propanamide;

2-(3-fluoro-4-(4-fluorophenyl)benzylamino)-2-methyl-propanamide;

2-(4-(2-pyrimidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-quinolinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(N, N-diphenylamino)benzylamino)-2-methyl-propanamide;

2-(4-diphenylmethoxy)benzylamino-2-methyl-propanamide; and

2-(4-triphenylmethoxy)benzylamino-2-methyl-propanamide.

Since the compounds of Formula **I** and **II** are blockers of sodium (Na^+) channels, a number of diseases and conditions mediated by sodium ion influx can be treated employing these compounds. Therefore, the invention is related to a method of treating, preventing or ameliorating neuronal loss associated with stroke, global and focal ischemia, CNS trauma, hypoglycemia and surgery, spinal cord trauma; as well as treating or ameliorating

neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, treating or ameliorating anxiety, convulsions, glaucoma, migraine headache, and muscle spasm. The compounds of Formula **I** and **II** are also useful as antimanic depressants, as local anesthetics, and as antiarrhythmics; as well as for treating, preventing or ameliorating pain including surgical, chronic and neuropathic pain. In each instance, the methods of the present invention require administering to an animal in need of such treatment an effective amount of a sodium channel blocker of the present invention, or a pharmaceutically acceptable salt or prodrug thereof.

The present invention is also directed to novel compounds within the scope of Formula **II**. These compounds include those compounds of Formula **II** where:

R_1, R_2, R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R_5, R_6 and R_7 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R_5, is defined as above, and R_6 and R_7 together with the nitrogen atom to which they are attached form a heterocycle, including piperidine, piperazine, morpholine;

A_1 and A_2 are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR_8, CH_2, C(O), $NR_8C(O)$, $C(O)NR_8$, SO, SO_2 or a covalent bond; where

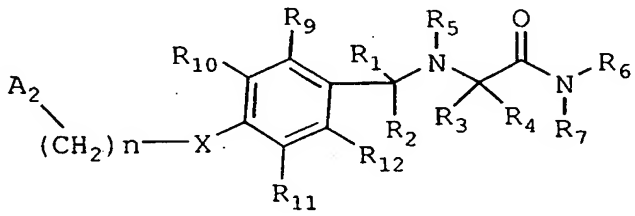
R_8 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

n is 0, 1, 2 or 3.

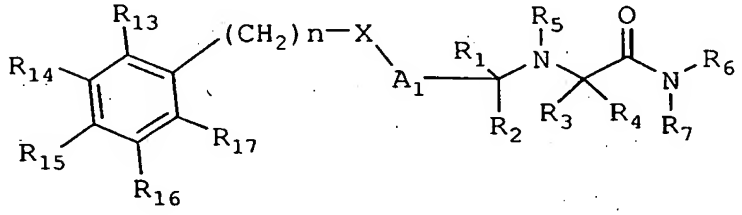
provided that:

when X is O, S, CH_2 or NH; R_1 and R_2 are hydrogen, R_3 and R_4 are methyl, then A_1 and A_2 are not both phenyl, with A_2 optionally substituted by one or two non-hydrogen substituents.

Specifically, preferred substituted 2-aminoacetamides are represented by Formulae **III-VIII**. In particular, a preferred embodiment is represented by Formulae **III** and **IV**:



III



IV

or a pharmaceutically acceptable salt or prodrug thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, n, A_1 and A_2 are as defined previously with respect to Formula **II**; and

R_9, R_{10}, R_{11} and R_{12} independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

R_9 and R_{10} or R_{11} and R_{12} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle. Examples of bridges formed by R_9 and R_{10} or R_{11} and R_{12} taken together are —OCH_2O—, -OCF_2O—, —$(CH_2)_3$—, —$(CH_2)_4$—, —OCH_2CH_2O—, —$CH_2N(R_{18})CH_2$—,

—$CH_2CH_2N(R_{18})CH_2$—, —$CH_2N(R_{18})CH_2CH_2$— and —CH=CH—CH=CH-; where R_{18} is hydrogen, alkyl or cycloalkyl;

provided that when A_2 in Formula **III** is an optionally substituted phenyl, then R_9 and R_{10} or R_{11} and R_{12} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle.

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

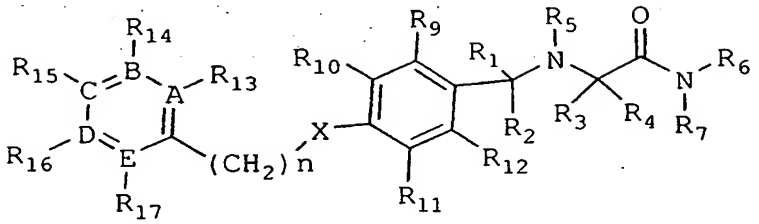
one of R_{13} and R_{14}, or R_{14} and R_{15}, or R_{15} and R_{16}, or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle. Examples of bridges formed by R_{13} and R_{14}, or R_{14} and R_{15}, or R_{15} and R_{16}, or R_{16} and R_{17} taken together are —OCH_2O—, -OCF_2O—, —$(CH_2)_3$—, —$(CH_2)_4$—, —OCH_2CH_2O—, —$CH_2N(R_{18})CH_2$—, —$CH_2CH_2N(R_{18})CH_2$—, —$CH_2N(R_{18})CH_2CH_2$— and —CH=CH—CH=CH-; where R_{18} is hydrogen, alkyl or cycloalkyl.

provided that when A_1 in Formula **IV** is an optionally substituted phenyl, then R_{13} and R_{14}, or R_{14} and R_{15}, or R_{15} and R_{16}, or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle.

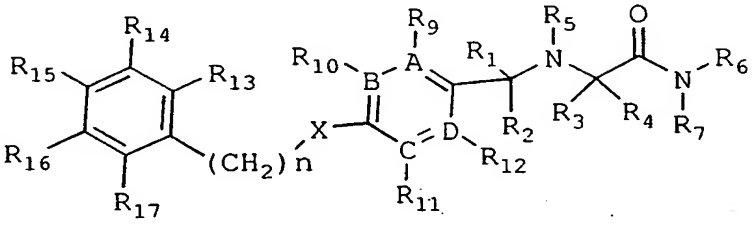
Preferred values of A_2 in Formula **III** include furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, indanyl, tetrahydronaphthyl, and naphthyl.

Preferred values of A_1 in Formula **IV** include furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, indanyl, tetrahydronaphthyl and naphthyl.

Another preferred embodiment of the invention includes substituted 2-aminoacetamides represented by Formula **V** and Formula **VI**:



V



VI

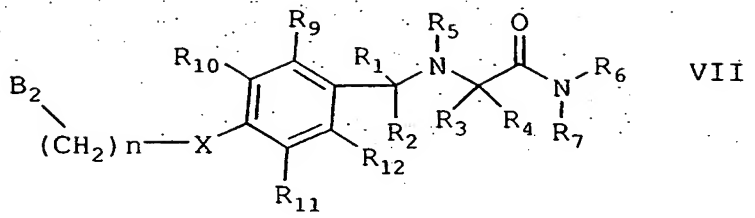
or a pharmaceutically acceptable salt or prodrug thereof, wherein

R_1-R_7, R_9-R_{12}, R_{13}-R_{17}, n and X are as defined previously with respect to Formulae **II**, **III** and **IV**; and

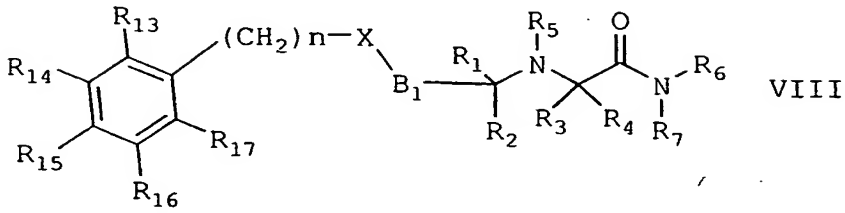
A, B, C, D and E are independently nitrogen or carbon, provided that no more than three of A, B, C, D and E are nitrogen, and there is no substituent, except for oxygen (when the nitrogen is present as a N-oxide), present on A, B, C, D or E when said A, B, C, D or E represents nitrogen.

Preferred compounds of Formula V are those where one, two or three of A through E are nitrogens. Preferred compounds of Formula VI are those where one or two of A through D are nitrogens.

Another preferred embodiment of the invention includes substituted 2-aminoacetamide represented by Formula **VII** and Formula **VIII**:



VII



VIII

or a pharmaceutically acceptable salt or prodrug thereof, wherein

R_1-R_7, R_9-R_{12}, R_{13}-R_{17}, n and X are as defined previously with respect to Formulae **II**, **III** and **IV**; and

B_1 is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle; and

B_2 is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle.

Preferred B_1 and B_2 independently include cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl and piperidinyl.

Generally, preferred compounds of Formulae **II-VIII** are those compounds where R_1 and R_2 is hydrogen or alkyl, more preferably hydrogen, methyl or ethyl, and where R_3 and R_4 are independently hydrogen or C_{1-4} alkyl.

Preferred values of X in Formulae **II-VIII** are O and S.

Preferred values of R_5-R_7 with respect to Formulae **II-VIII** are hydrogen or C_{1-4} alkyl.

Preferred values of R_9-R_{12}, and R_{13}-R_{17}, with respect to Formulae **II-VIII** include hydrogen, halo, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_4-C_7 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl(C_1-C_6)alkyl, C_6-C_{10} aryl(C_2-C_6)alkenyl, C_6-C_{10} aryl(C_2-C_6)alkynyl, C_1-C_6 hydroxyalkyl, nitro,

amino, ureido, cyano, C_1-C_6 acylamido, hydroxy, thiol, C_1-C_6 acyloxy, azido, C_1-C_6 alkoxy, and carboxy. Alternatively, R_9 and R_{10} or R_{11} and R_{12}, or two adjacent R_{13} through R_{17} can form a bridge selected from the group consisting of —OCH_2O—, —$(CH_2)_3$—, —$(CH_2)_4$—, —OCH_2CH_2O—, -$CH_2N(R_{18})CH_2$-, —$CH_2CH_2N(R_{18})CH_2$—, —$CH_2N(R_{18})CH_2CH_2$—, and —CH=CH-CH=CH—, where R_{18} is hydrogen or C_1-C_6 alkyl. Most preferably, at least one, two or three of R_9, R_{10}, R_{11}, R_{12} are hydrogen. Most preferably, at least one, two or three of R_{13} through R_{17} are hydrogen.

With respect to the novel methods of treatment of the present invention, an additional preferred subset of substituted 2-aminoacetamide compounds includes compounds of Formula **II**, wherein A_1 and A_2 are phenyl moieties, that A_2 is substituted by one or two substituents independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-4} alkoxy, or trifluoromethyl; each of R_1 and R_2 are hydrogen; R_3 and R_4 are methyl; and R_5-R_7 are independently C_{1-6} alkyl or C_{3-7} cycloalkyl.

Useful compounds in this aspect of the present invention include:

2-(4-(2-fluorobenzyloxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxyphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxybenzyloxy)benzylamino)-2-methyl-propanamide;

2-(4-cyclohexyloxybenzylamino)-2-methyl-propanamide;

2-(4-(5,6,7,8-tetrahydro-2-naphthoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-adamantanoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-Chloro-2-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-bromo-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-nitrophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-tetrahydropyranoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,5-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-chlorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-methylphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-chloro-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(5-indanoxy)benzylamino)-2-methyl-propanamide;

2-(4-cycloheptoxybenzylamino)-2-methyl-propanamide;

2-(4-(1-methyl-4-piperidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(exo-2-norbornoxy)benzylamino)-2-methyl-propanamide;

2-(3-(4-fluorophenoxy)-5-pyridylmethylamino)-2-methyl-propanamide;

2-(4-(4-pyridinoxy)benzylamino)-2-methyl-propanamide;

2-(3-fluoro-4-(4-fluorophenyl)benzylamino)-2-methyl-propanamide;

2-(4-(2-pyrimidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-quinolinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(N, N-diphenylamino)benzylamino)-2-methyl-propanamide;

2-(4-diphenylmethoxy)benzylamino-2-methyl-propanamide; and

2-(4-triphenylmethoxy)benzylamino-2-methyl-propanamide.

Useful aryl groups are C_{6-14} aryl, especially C_{6-10} aryl. Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.

Useful cycloalkyl groups include C_{3-8} cycloalkyl groups. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and cycloheptyl.

Useful saturated or partially saturated carbocyclic groups are cycloalkyl groups as defined above, as well as cycloalkenyl groups, such as cyclopentenyl, cycloheptenyl and cyclooctenyl.

Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

Useful alkyl groups include straight-chained and branched C_{1-10} alkyl groups, more preferably C_{1-6} alkyl groups. Typical C_{1-10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, 3-pentyl, hexyl and octyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on the benzene ring of the compounds of the invention.

Useful alkenyl groups include C_{2-6} alkenyl groups, preferably C_{2-4} alkenyl. Typical C_{2-4} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec.*-butenyl.

Useful alkynyl groups include C_{2-6} alkynyl groups, preferably C_{2-4} alkynyl. Typical C_{2-4} alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

Useful arylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned C_{6-14} aryl groups. Typical groups include benzyl, phenethyl and naphthylmethyl.

Useful arylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Useful arylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned C_{6-14} aryl groups. Typical groups include phenylethynyl and phenylpropynyl.

Useful cycloalkylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned cycloalkyl groups.

Useful haloalkyl groups include C_{1-10} alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g. fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

Useful hydroxyalkyl groups include C_{1-10} alkyl groups substituted by hydroxy, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

Useful alkoxy groups include oxygen substituted by one of the C_{1-10} alkyl groups mentioned above.

Useful alkylthio groups include sulphur substituted by one of the C_{1-10} alkyl groups mentioned above.

Useful acylamino groups are any C_{1-6} acyl (alkanoyl) attached to an amino nitrogen, e.g. acetamido, propionamido, butanoylamido, pentanoylamido, hexanoylamido as well as aryl-substituted C_{2-6} substituted acyl groups.

Useful acyloxy groups are any C_{1-6} acyl (alkanoyl) attached to an oxy (-O-) group, e.g. acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

Useful saturated or partially saturated heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperizinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl and pyrazolinyl groups.

Useful heterocycloalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned heterocyclic groups.

Useful heteroaryl groups include any one of the following: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, 5a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, 4-nitrobenzofurazan, benzimidazolyl, 2-oxindolyl and 2-oxobenzimidazolyl. Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the

form of an N-oxide, e.g. a pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide and the like.

Useful heteroarylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful heteroarylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful heteroarylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful amino groups include $-NH_2$, $-NHR_{19}$, and $-NR_{19}R_{20}$, wherein R_{19} and R_{20} are C_{1-10} alkyl or cycloalkyl groups as defined above.

Useful aminocarbonyl groups are carbonyl groups substituted by $-NH_2$, $—NHR_{19}$, and $—NR_{19}R_{20}$, wherein R_{19} and R_{20} are C_{1-10} alkyl groups.

Optional substituents on any of the aryl, heterocyclic, heteroaryl, and cycloalkyl rings in Formulae **II-VIII** include any one of halo, haloalkyl, aryl, heterocycle, cycloalkyl, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, aminocarbonyl, and alkylthiol groups mentioned above. Preferred optional substituents include: halo, haloalkyl, hydroxyalkyl, aminoalkyl, nitro, alkyl, alkoxy and amino.

Certain of the compounds of Formula **II** may exist as optical isomers and the invention includes both the racemic mixtures of such optical isomers as well as the individual entantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, phosphate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, acetic acid, dichloroacetic acid and oxalate.

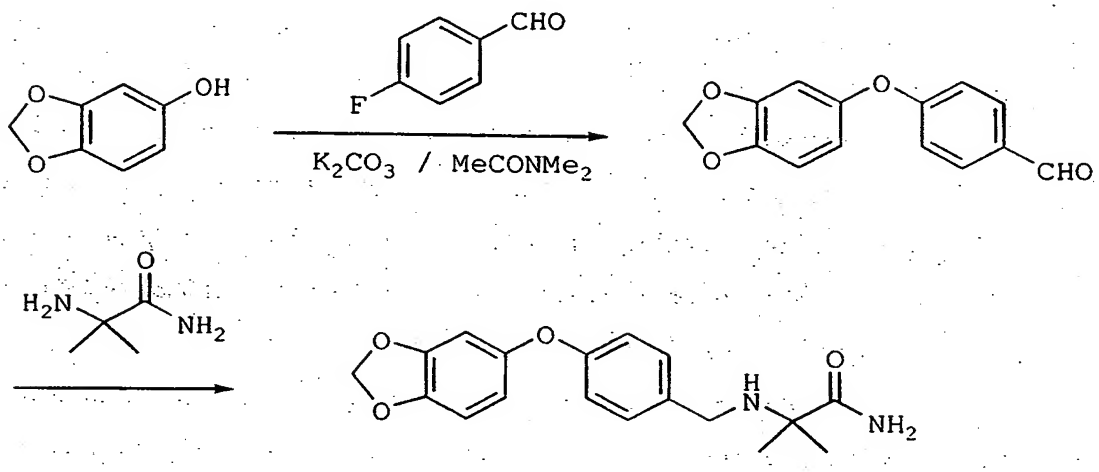
Examples of prodrugs include esters or amides of Formula **II** with R_1-R_7 as hydroxyalkyl or aminoalkyl, and these may be prepared by reacting such compounds with anhydrides such as succinic anhydride.

The invention is also directed to a method for treating disorders responsive to the blockade of sodium channels in animals suffering thereof. Particular preferred embodiments of the substituted 2-aminoacetamide for use in method of this invention are represented by previously defined Formula **II**.

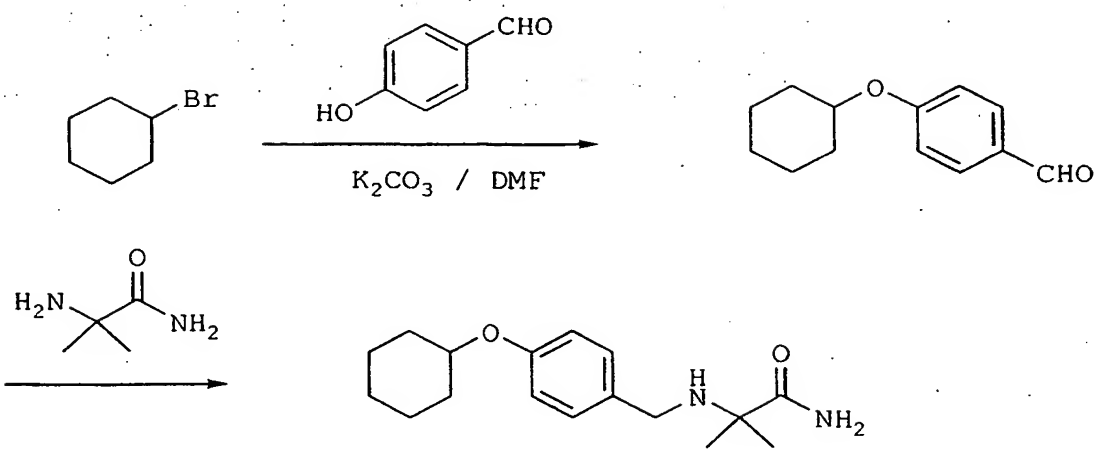
The compounds of this invention may be prepared using methods known to those skilled in the art, or by the novel methods of this invention. The methods described in PCT published application WO97/05102, can be employed to synthesize compounds within the scope of the invention.

Compounds with Formulae **II-VIII** can be prepared as illustrated by exemplary reactions in Schemes 1-5.

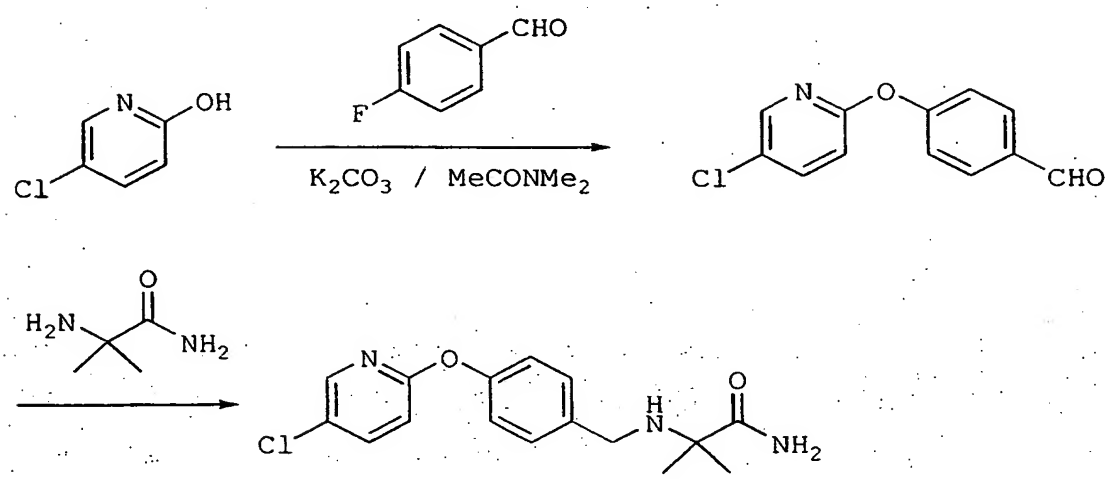
Scheme 1



Scheme 2

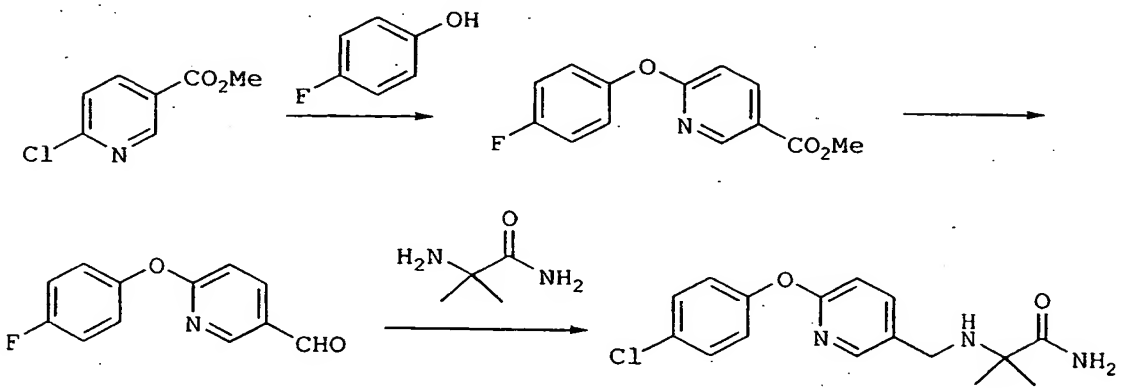


Scheme 3

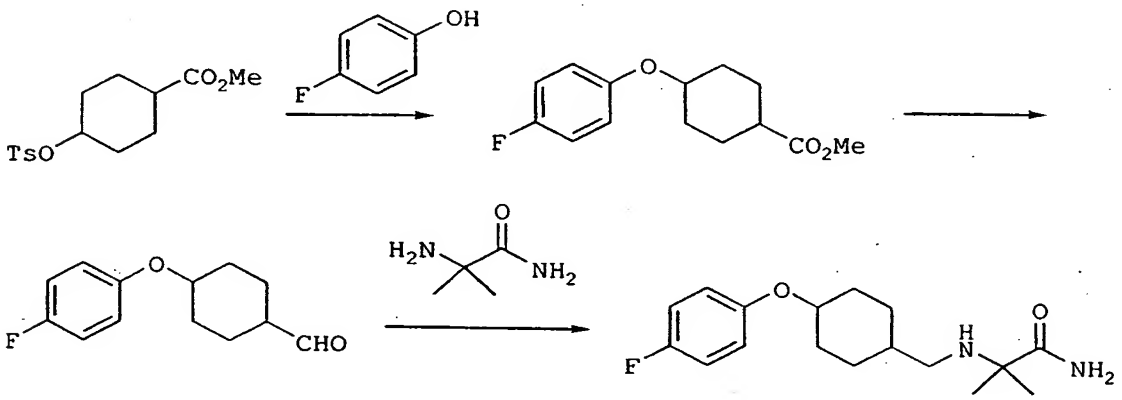


5

Scheme 4



Scheme 5



The compounds of the present invention were assessed by electrophysiological assays in dissociated hippocampal neurons for sodium channel blocker activity. These compounds also could be assayed for binding to the neuronal voltage-dependent sodium channel using rat forebrain membranes and [^{3}H]BTX-B.

Sodium channels are large transmembrane proteins that are expressed in various tissues. They are voltage sensitive channels and are responsible for the rapid increase of Na^+ permeability in response to depolarization associated with the action potential in many excitable cells including muscle, nerve and cardiac cells.

One aspect of the present invention is the discovery of the mechanism of action of the compounds herein described as specific Na^+ channel blockers.

In one aspect of the present invention it has been discovered that compounds disclosed in international published application WO 97/05102 are specific Na^+ channel blockers. Based upon the discovery of this mechanism, these compounds, as well as novel compounds described herein, are contemplated to be useful in treating or preventing neuronal loss due to focal or global ischemia, and in treating or preventing neurodegenerative disorders including ALS, anxiety, and epilepsy. They are also expected to be effective in treating, preventing or ameliorating neuropathic pain, surgical pain and chronic pain. The compounds are also expected to be useful as antiarrhythmics, anesthetics and antimanic depressants.

The present invention is directed to compounds of Formulae **II** that are blockers of voltage-sensitive sodium channels. According to the present invention, those compounds having preferred sodium channel blocking properties exhibit an IC_{50} of about 100 μM or less in the electrophysiological assay described herein. Preferably, the compounds of the present invention exhibit an IC_{50} of 10 μM or less. Most preferably, the compounds of the present invention exhibit an IC_{50} of about 1.0 μM or less. Substituted 2-aminoacetamide disclosed in WO 97/05102, as well as novel compounds of the present invention, may be tested for their Na^+ channel blocking activity by the following electrophysiological and binding assays.

Electrophysiological Assay:

Cell preparation: Acute cultures of rat hippocampal neurons were prepared daily using a modification of procedures described previously (Kuo and Bean, *Mol. Pharm. 46*:716-725 (1994)). Briefly, hippocampi were isolated from 3-11 day old rat pup brains (Sprague-Dawley; Charles River) and were sectioned, by hand, into 0.5 - 1 mm thick transverse slices (Whittemore and Koerner, *Eur. J. Pharm. 192*:435-438 (1991)). Slices were incubated for at least 30 min at room temperature (20 - 24°C) in an oxygenated medium (124 mM NaCl, 3.3 mM KCl, 2.4 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.2

mM KH_2PO_4, 26 mM $NaHCO_3$, pH = 7.4) continuously bubbled with 5% CO_2 / 95 % O_2. Prior to recording, 4-5 slices were transferred to an oxygenated dissociation medium (82 mM $NaSO_4$, 30 mM K_2SO_4, 3 mM $MgCl_2$, 2 mM HEPES, 26 mM $NaHCO_3$, 0.001% phenol red, pH = 7.4) containing 3 mg / mL protease XXIII (Sigma, St. Louis, MO) and incubated for 10 - 15 min at 37°C, while continuously bubbling with 5 % CO_2 / 95 % O_2. Enzymatic digestion was terminated by transferring the slices to dissociation medium without bicarbonate, supplemented with 1 mg / mL bovine serum albumin and 1 mg / mL trypsin inhibitor (Sigma, St. Louis, MO). Slices were then transferred to a 35 mm culture dish containing dissociation medium without bicarbonate, and triturized with a fire-polished glass Pasteur pipette to release single cells. Cells were allowed to settle in this dish for ~30 minutes and were then used for making electrical recordings.

Patch-clamp recordings of voltage-sensitive Na^+ currents: Whole-cell voltage-clamp recordings were made using conventional patch-clamp technique (Hamill *et al., Pfluegers Arch. 391*:85-100 (1981)) with an Axopatch 200A amplifier (Axon Instruments, Foster City, CA). Recordings were made within 2-3 hours after neuron dissociation. The recording chamber was continuously superfused with Tyrode's solution (156 mM NaCl, 3.5 mM KCl, 2 mM $CaCl_2$, 5 mM $NaHCO_3$, 10 mM HEPES, 10 mM glucose, pH 7.4) at a speed of about 1 ml/min. Thin-walled pipettes were pulled from 100-µl Clay Adams Accu-Fill 90 Micropet disposable pipettes (Becton, Dickenson and Company, Parsipanny, NJ), fire-polished and sylgarded (Dow-Corning, Midland, MI). The pipette resistances ranged from 1 to 3 MΩ when the pipettes were filled with internal solution containing (in mM): 130 CsF, 20 NaCl, 1 $CaCl_2$, 2 $MgCl_2$, 10 EGTA, 10 HEPES, pH adjusted to 7.4 with CsOH. Drugs and intervening wash-outs were applied through a linear array of flow pipes (Drummond Microcaps, 2-µl, 64-mm length). Compounds are dissolved in dimethylsulfoxide (DMSO) to make a 10 mM stock solution, which was subsequently diluted into Tyrode's solution to give final concentrations of 0.1-20 µM. At the highest (1%) concentration, DMSO

inhibited the size of Na^+ current only slightly. Currents were recorded at room temperature (22-25°C), filtered at 5 kHz with 4-pole Bessel filter, digitized at 20-50-μs intervals, and stored using Digidata 1200 analog/digital interface with Pclamp6/Clampex software (Axon Instruments). Residual series resistance ranged from 0.4 to 0.8 MΩ after partial compensation (typically ~90%). The inhibitory potency of drugs was assessed by measuring reductions in the peak amplitude of Na^+ currents induced by increasing concentrations of compounds tested. Na^+ currents were elicited by stepping membrane voltage from holding potentials over the range -100 mV to -50 mV, to a pulse potential of -10 mV. The test pulse duration was 5-10 msec, repeated at a frequency $\leq$ 1 Hz. Concentration-inhibition curves were fitted with equation 1:

$$I/I_{control} = 1/(1 + ([compound]/IC_{50})) \qquad \text{Eq. 1}$$

where $I_{control}$ is the maximal Na^+ current in the absence of antagonist, [compound] is the drug concentration, and IC_{50} is the concentration of compound that produces half maximal inhibition.

Binding Assay:

The ability of compounds of the present invention to modulate either site 1 or site 2 of the Na^+ channel was determined following the procedures fully described in Yasushi, *J. Biol. Chem. 261*:6149-6152 (1986) and Creveling, *Mol. Pharmacol. 23*:350-358 (1983), respectively. Rat forebrain membranes were used as sources of Na^+ channel proteins. The binding assays were conducted in 130 μM choline chloride at 37°C for 60-minute incubation with [^{3}H] saxitoxin and [^{3}H] batrachotoxin as radioligands for site 1 and site 2, respectively.

The compounds of the present invention may be tested for *in vivo* anticonvulsant activity after iv or ip injection using a number of anticonvulsant

tests in mice (audiogenic seizure model in DBA-2 mice, pentylenetetrazol-induced seizures in mice, maximum electroshock seizure test (MES)).

The compounds may be tested for their neuroprotective activity after focal and global ischemia produced in rats or gerbils according to the procedures described in Buchan *et al.* (*Stroke*, Suppl. 148-152 (1993)) and Sheardown *et al.* (*Eur. J. Pharmacol. 236*:347-353 (1993)) and Graham *et al.* (*J. Pharmacol. Exp. Therap. 276*:1-4 (1996)).

The compounds may be tested for their neuroprotective activity after traumatic spinal cord injury according to the procedures described in Wrathall *et. al.* (*Exp. Neurology 137*:119-126 (1996)) and Iwasaki *et. al.* (*J. Neuro Sci. 134*:21-25 (1995)).

Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for epilepsy, neurodegenerative diseases, anesthesia, arrhythmia, manic depression, and pain. For intramuscular injection, the dose is generally about one-half of the oral dose.

In the method of treatment or prevention of neuronal loss in global and focal ischemia, brain and spinal cord trauma, hypoxia, hypoglycemia, status epilepsy and surgery, the compound can be administrated by intravenous injection at a dose of about 0.025 to about 10 mg/kg.

The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the particular 2-aminoacetamide of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, and the like. Basic salts are formed by mixing a solution of the particular 2-aminoacetamide of the present invention with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage

administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetyl-cellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example,

for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and

adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

Example 1

2-(4-(2-Fluorobenzyloxy)benzylamino)-2-methyl-propanamide as Na^+ channel blocker

2-(4-(2-Fluorobenzyloxy)benzylamino)-2-methyl-propanamide was tested in the electrophysiological and binding assays described above and produced dose-dependent inhibition of voltage-gated Na^+ currents recorded in acutely dissociated rat hippocampal neurons. The blocking effect of this compound on Na^+ currents was highly sensitive to the holding voltage. For example, at concentrations between 0.1 - 10 μM, 2-(4-(2-fluorobenzyloxy)benzylamino)-2-methyl-propanamide had very little effect on Na^+ currents activated from a holding membrane voltage of -100 mV, but inhibited currents with increasing potency as the holding potential was progressively depolarized. The most potent block in these studies was seen at a membrane holding voltage of -65 mV. The decrease in current was due to steady-state inactivation of the Na^+ channels.

This data indicates that 2-(4-(2-fluorobenzyloxy)benzylamino)-2-methyl-propanamide binds to voltage-sensitive Na^+ channels in their inactivated states and has weak potency towards Na^+ channels in their resting states (Ragsdale *et al., Mol. Pharmacol. 40*:756-765 (1991); Kuo and Bean, *Mol. Pharmacol. 46*:716-725 (1994)). The apparent antagonist dissociation constant (K_d) of this compound for inactivated Na^+ channels is ~1.2 μM.

Example 2

2-(4-(3,4-Methylenedioxyphenoxy)benzylamino)-2-methyl-propanamide

a) 4-(3,4-Methylenedioxyphenoxy)benzaldehyde: A mixture of sesamol (5.13 g, 37.1 mmol), 4-fluorobenzaldehyde (4.0 mL, 37.3 mmol), potassium carbonate (6.21 g, 44.9 mmol) in *N,N*-dimethylacetamide (50 mL) was refluxed for 23 h. The mixture was added to water and extracted with an ethyl acetate/hexane solution. The organic layer was washed with aqueous sodium hydroxide (2 N), dried over sodium sulfate, and evaporated under reduced pressure to give crude product. The crude product was purified by flash chrmoatography to give a pink solid, which was decolorized by refluxing with activated charcoal in chloroform for 1 h. Filtration through Celite and removal of the chloroform in vacuo gave the desired aldehyde. ^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.7Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.58-6.54 (m, 1H), 6.02 (s, 2H).

b) 2-Amino-2,2-dimethylethanamide: A solution of HCl in dioxane (4.0 M), methanol (54 ml) and aminoisobutyric acid (11.7 g, 0.114 mol) was refluxed for 6 h. Once at rt, the solution was concentrated to a white solid. NMR of the solid showed that the solid was a mixture of aminoisobutyric acid and methyl 2-amino-2,2-dimethylacetate. This crude intermediate was heated to 50 degree Celsius in aqueous ammonium hydroxide (29%, 140 ml) in a sealed tube for 24 hours. The solution was cooled to room temperature, then evaporated under reduced pressure to give a white solid. ^{1}H NMR of the solid showed that the white solid contained 40% of the title product. ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 2H), 7.48 (s, 2H), 1.27 (s, 6H).

c) 2-(4-(3,4-Methylenedioxyphenoxy)benzylamino)-2-methylpropanamide: To a solution of 4-(3,4-methylenedioxyphenoxy)benzaldehyde (0.51 g, 0.21 mmol) in 30 mL of anhydrous ethanol was added 3Å molecular sieves (1 g), and 2-amino-2,2-dimethylethanamide (1.67 g, 40% by weight by ^{1}H

NMR, 0.49 mmol). After stirring for 24 h, the resulting mixture was treated with sodium cyanoborohydride (95%; 1.0 g, 16 mmol). After stirring for an additional 8 h, the reaction was quenched with water. The aqueous layer was extracted three times with an ethyl acetate/hexane mixture. The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to give 77 mg (11%) of the title product, mp = 123-124 °C. ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 5.96 (s, 2H), 5.47 (bs, 2H), 3.66 (s, 2H), 1.42 (s, 6H).

The following compounds were prepared similiarly:

2-(4-(4-Fluorophenoxy)benzylamino)-2-methylpropanamide: mp = 103-106 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 7.02-6.92 (m, 6H), 5.6 (bs, 2H), 3.68 (s, 2H), 1.43 (s, 6H).

2-(4-(2,4-Difluorophenoxy)benzylamino)-2-methylpropanamide: TLC solvent: 60:40 hexane/ethylacetate; TLC R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 7.27-6.85 (m, 7H), 5.5 (bs, 2H), 3.67 (s, 2H), 1.42 (s, 6H).

2-(4-(5-Indanoxy)benzylamino)-2-methylpropanamide: mp = 81-83 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.87 (s, 1H), 6.78 (d, J = 6.0 Hz, 1H), 5.5 (bs, 2H), 3.66 (s, 2H), 2.88 (t, J = 6.9 Hz, 4H), 2.19-2.0 (m, 2H), 1.41 (s, 6H).

The following compounds can be similarly prepared by allowing the appropriate aldehyde precursor to react with 2-methylpropanamide as described above:

2-(4-(3,4-Methylenedioxyphenoxy)benzylamino)-2-methylpropanamide

2-(4-Cyclohexyloxybenzylamino)-2-methylpropanamide

2-(4-(5,6,7,8-tetrahydro-2-naphthoxy)benzylamino)-2-methylpropanamide

2-(4-(2-Adamantanoxy)benzylamino)-2-methylpropanamide

2-(4-(4-Chloro-2-fluorophenoxy)benzylamino)-2-methylpropanamide

2-(4-(2-Chloro-4-fluorophenoxy)benzylamino)-2-methylpropanamide

2-(4-(3,4-Difluorophenoxy)benzylamino)-2-methylpropanamide

2-(4-(3,5-Difluorophenoxy)benzylamino)-2-methylpropanamide

2-(4-(6-Bromo-4-fluorophenoxy)benzylamino)-2-methylpropanamide

2-(4-(4-Nitrophenoxy)benzylamino)-2-methylpropanamide

2-(4-(4-Tetrahydropyranoxy)benzylamino)-2-methylpropanamide

2-(4-(4-Chlorophenoxy)benzylamino)-2-methylpropanamide

2-(4-(4-Methylphenoxy)benzylamino)-2-methylpropanamide

2-(4-Cycloheptoxybenzylamino)-2-methylpropanamide

2-(4-(1-Methyl-4-piperidinoxy)benzylamino)-2-methylpropanamide

2-(4-(exo-2-norbornoxy)benzylamino)-2-methylpropanamide

2-(3-(4-Fluorophenoxy)-5-pyridylmethylamino)-2-methylpropanamide

2-(4-(4-Pyridinoxy)benzylamino)-2-methylpropanamide

2-(3-Fluoro-4-(4-fluorophenyl)benzylamino)-2-methylpropanamide

2-(4-(2-Pyrimidinoxy)benzylamino)-2-methylpropanamide

2-(4-(6-Quinolinoxy)benzylamino)-2-methylpropanamide

2-(4-(N,N-diphenylamino)benzylamino)-2-methylpropanamide

2-(4-Diphenylmethoxy)benzylamino)-2-methylpropanamide

2-(4-Triphenylmethoxy)benzylamino)-2-methylpropanamide

2-(4-(3,4-Methylenedioxybenzyloxy)benzylamino)-2-methylpropanamide

The ability of selected 2-methylpropanamide derivatives to block maximal electroshock-induced seizures (MES) was determined by the following procedure.

Seizures were induced by application of current (50 mA, 60 pulses/sec, 0.8 msec pulse width, 1 sec duration, D.C.) using a Ugo Basile ECT device (model 7801). Mice were restrained by gripping the loose skin on their dorsal surface and saline-coated corneal electrodes were held lightly against the two cornea. Current was applied and mice were observed for a period of up to 30 sec for the occurrence of a tonic hindlimb extensor response. A tonic seizure was defined as a hindlimb extension in excess of 90 degrees from plane of the body. The 2-methylpropanamides tested were administered iv to mice 10 min before the test procedure.

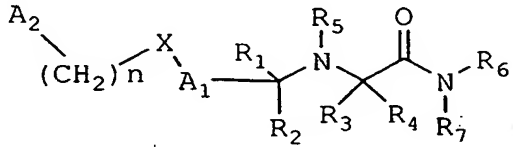
Table 1. Activity of Substituted Benzylamino 2-methylpropanamide in MES iv in mouse

Substituent	Example No.	iv MES activity (number protected/number screened)
4-fluorophenoxy	2	8/8
3,4-methylenedioxyphenoxy	2	8/8
2,4-difluorophenoxy	2	8/8
5-indanoxy	2	1/8

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A method of treating or ameliorating pain in a mammal, comprising administering to a mammal in need of such treatment an effective amount of a compound having the Formula **II**:



II

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1 R_2, R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R_5, R_6 and R_7 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R_5, is defined as above, and R_6 and R_7 together with the nitrogen atom to which they are attached form a heterocycle;

A_1 and A_2 are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR_8, CH_2, C(O), $NR_8C(O)$, $C(O)NR_8$, SO, SO_2 or a covalent bond; where

R_8 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

n is 0, 1, 2 or 3.

2. The method according to claim 1, wherein A1 and A2 are both optionally substituted aryl moieties.

3. The method according to claim 1, wherein

A_1 and A_2 are phenyl moieties, that A_2 is optionally substituted by one or two substituents independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-4} alkoxy or trifluoromethyl;

R_1 and R_2 are hydrogen;

R_3 and R_4 are methyl;

R_5, R_6 and R_7 are independently hydrogen, C_{1-6} alkyl, or C_{3-7} cycloalkyl; and

X is O, S, CH_2, or NH.

4. The method according to claim 1, wherein said compound is selected from the group consisting of:

2-(4-(2-fluorobenzyloxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxyphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxybenzyloxy)benzylamino)-2-methyl-propanamide;

2-(4-cyclohexyloxybenzylamino)-2-methyl-propanamide;

2-(4-(5,6,7,8-tetrahydro-2-naphthoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-adamantanoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-Chloro-2-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-bromo-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-nitrophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-tetrahydropyranoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,5-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-chlorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-methylphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-chloro-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(5-indanoxy)benzylamino)-2-methyl-propanamide;

2-(4-cycloheptoxybenzylamino)-2-methyl-propanamide;

2-(4-(1-methyl-4-piperidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(exo-2-norbornoxy)benzylamino)-2-methyl-propanamide;

2-(3-(4-fluorophenoxy)-5-pyridylmethylamino)-2-methyl-propanamide;

2-(4-(4-pyridinoxy)benzylamino)-2-methyl-propanamide;

2-(3-fluoro-4-(4-fluorophenyl)benzylamino)-2-methyl-propanamide;

2-(4-(2-pyrimidinoxy)benzylamino)-2-methyl-propanamide;

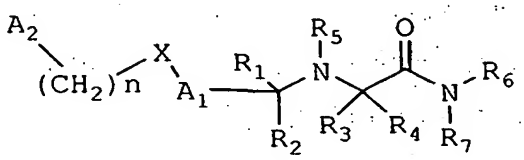
2-(4-(6-quinolinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(N, N-diphenylamino)benzylamino)-2-methyl-propanamide;

2-(4-diphenylmethoxy)benzylamino-2-methyl-propanamide; and

2-(4-triphenylmethoxy)benzylamino-2-methyl-propanamide.

5. A method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating neurodegenerative conditions; treating, preventing or ameliorating pain; treating, preventing or ameliorating manic depression; providing local anesthesia; or treating arrhythmias, comprising administering to a mammal in need of such treatment an effective amount of a compound having the Formula **II**:



II

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1, R_2, R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R_5, R_6 and R_7 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R_5, is defined as above, and R_6 and R_7 together with the nitrogen atom to which they are attached form a heterocycle;

A_1 and A_2 are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR_8, CH_2, C(O), $NR_8C(O)$, $C(O)NR_8$, SO, SO_2 or a covalent bond; where

R_8 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

n is 0, 1, 2 or 3;

provided that when X is O, S, CH_2 or NH; R_1 and R_2 are hydrogen, R_3 and R_4 are methyl or ethyl, then A_1 and A_2 are not both phenyl.

6. The method according to claim 5, wherein said method is for treating, preventing or ameliorating pain and said pain is one of neuropathic pain, surgical pain or chronic pain.

7. The method according to claim 6, wherein:

A_1 and A_2 are phenyl moieties, wherein A_1 is substituted by one or two substituents independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-4} alkoxy and trifluoromethyl;

R_1 and R_2 are hydrogen;

R_3 and R_4 are methyl;

R_5, R_6 and R_7 are independently hydrogen, C_{1-6} alkyl, or C_{3-7} cycloalkyl; and

X is O, S, CH_2, or NH. --

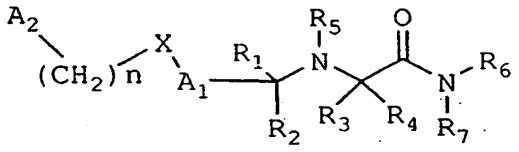
8. The method of claim 5, wherein:

A_1 is an optionally substituted aryl group selected from the group consisting of phenyl and naphthyl, and A_2 is an optionally substituted heteroaryl or aryl group selected from the group consisting of pyridyl, pyrimidinyl, 1,3,5-triazinyl, furanyl, thiophenyl, naphthyl, quinolyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, indanyl, tetrahydronaphthyl and quinoxalinyl.

9. The method of claim 5, wherein

A_1 is an optionally substituted aryl group selected from the group consisting of phenyl or naphthyl, and A_2 is an optionally substituted carbocycle or heterocycle selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, cyclohexenyl, adamantyl, *exo*-norbornyl and cyclopentenyl.

10. A compound having the Formula **II**:



II

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1 R_2, R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R_5, R_6 and R_7 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R_5, is defined as above, and R_6 and R_7 together with the nitrogen atom to which they are attached form a heterocycle;

A_1 and A_2 are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR_8, CH_2, C(O), $NR_8C(O)$, $C(O)NR_8$, SO, SO_2 or a covalent bond; where

R_8 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

n is 0, 1, 2 or 3.

provided that:

when X is O, S, CH_2 or NH; R_1 and R_2 are hydrogen, R_3 and R_4 are methyl or ethyl, then A_1 and A_2 are not both phenyl.

11. A compound according to claim 10, wherein

A_1 is phenyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen;

A_2 is pyridinyl, pyrimidinyl, 1,3,5-triazinyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, quinolinyl, quinoxalinyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen; and

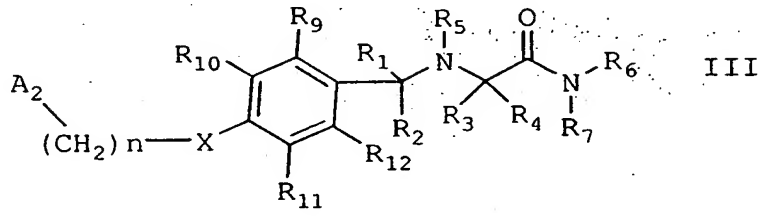
X is O or S.

12. A compound according to claim 10, wherein

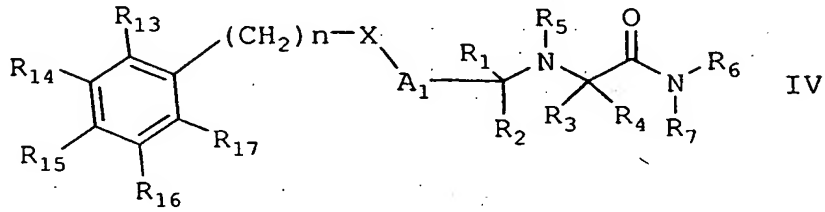
A_1 is pyridinyl, pyrimidinyl, 1,3,5-triazinyl, quinolinyl, furanyl, thiophenyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen, and

A_2 is phenyl, 3,4-methylenedioxyphenyl, 3,4-ethyelendioxyphenyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen.

13. A compound of claim 10, having Formula III or Formula IV:



III



IV

or a pharmaceutically acceptable salt or prodrug thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, n, A_1 and A_2 are as defined previously with respect to claim 10; and

R_9, R_{10}, R_{11} and R_{12} independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, hetroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

R_9 and R_{10} or R_{11} and R_{12} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle;

provided that when A_2 is an optionally substituted phenyl, then R_9 and R_{10} or R_{11} and R_{12} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle;

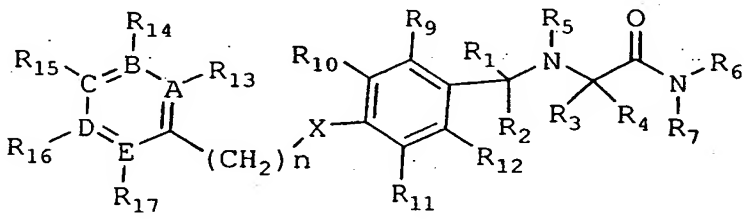
R_{13}, R_{14}, R_{15}, R_{16} and R_{17} independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl,

hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

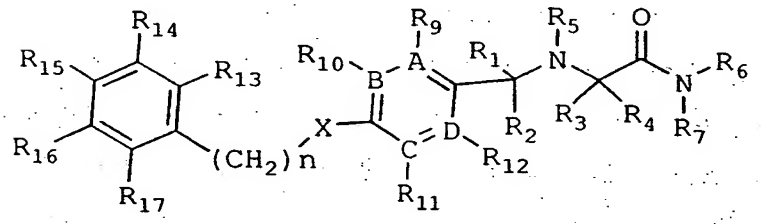
one of R_{13} and R_{14}, or R_{14} and R_{15}, or R_{15} and R_{16}, or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle;

provided that when A_1 is an optionally substituted phenyl, then R_{13} and R_{14}, or R_{14} and R_{15}, or R_{15} and R_{16}, or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle.

14. A compound of claim 13, having Formula V or Formula VI:



V



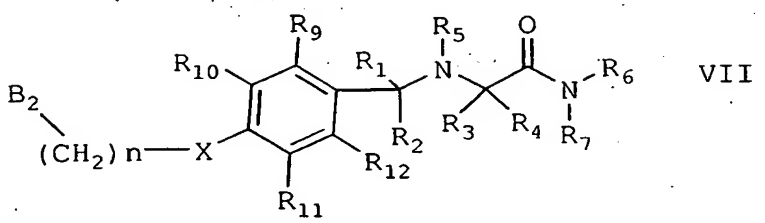
VI

or a pharmaceutically acceptable salt or prodrug thereof, wherein

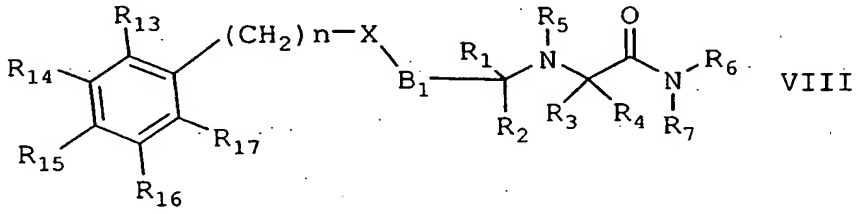
R_1-R_7, R_9-R_{12}, R_{13}-R_{17}, n and X are as defined previously with respect to claim 13; and

A, B, C, D and E are independently nitrogen or carbon, provided that no more than three of A, B, C, D and E are nitrogen, and there is no substituent, except for oxygen (when the nitrogen is present as a N-oxide), present on A, B, C, D or E when said A, B, C, D or E represents nitrogen.

15. A compound of claim 13, having the Formula VII or Formula VIII:



VII



VIII

or a pharmaceutically acceptable salt or prodrug thereof, wherein

R_1-R_7, R_9-R_{12}, R_{13}-R_{17}, n and X are as defined previously with respect to claim 13; and

B_1 is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle; and

B_2 is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle.

16. A compound according to claim 15, wherein B_1 is cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl or piperidinyl.

17. A compound according to claim 15, wherein B_2 is cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl or piperidinyl.

18. A compound according to claim 10, wherein said compound is

2-(4-(4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxyphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-methylenedioxybenzyloxy)benzylamino)-2-methyl-propanamide;

2-(4-cyclohexyloxybenzylamino)-2-methyl-propanamide;

2-(4-(5,6,7,8-tetrahydro-2-naphthoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-adamantanoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-Chloro-2-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,4-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-bromo-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-nitrophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-tetrahydropyranoxy)benzylamino)-2-methyl-propanamide;

2-(4-(3,5-difluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-chlorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(4-methylphenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(2-chloro-4-fluorophenoxy)benzylamino)-2-methyl-propanamide;

2-(4-(5-indanoxy)benzylamino)-2-methyl-propanamide;

2-(4-cycloheptoxybenzylamino)-2-methyl-propanamide;

2-(4-(1-methyl-4-piperidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(exo-2-norbornoxy)benzylamino)-2-methyl-propanamide;

2-(3-(4-fluorophenoxy)-5-pyridylmethylamino)-2-methyl-propanamide;

2-(4-(4-pyridinoxy)benzylamino)-2-methyl-propanamide;

2-(3-fluoro-4-(4-fluorophenyl)benzylamino)-2-methyl-propanamide;

2-(4-(2-pyrimidinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(6-quinolinoxy)benzylamino)-2-methyl-propanamide;

2-(4-(N, N-diphenylamino)benzylamino)-2-methyl-propanamide;

2-(4-diphenylmethoxy)benzylamino-2-methyl-propanamide; and

2-(4-triphenylmethoxy)benzylamino-2-methyl-propanamide.

19. A pharmaceutical composition, comprising the compound of any one of claims 10-18, and a pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24965

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/165
US CL :514/620, 357, 445, 471, 618
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/620, 357, 445, 471, 618

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEMICAL ABSTRACTS AND BEILSTEIN ON STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,449,692 A (VARASI et al.) 12 September 1995, col. 1, lines 36-68.	1,2
X	US 5,446,066 A (VARASI et al.) 29 August 1995, col. 1, lines 35-68.	1,2,5
X	WO 97/05102 A1 (PHARMACIA AND UPJOHN S.P.A.) 13 February 1997, pages 1-3, table 1.	1-4
X	US 5,236,957 A (DOSTERT et al.) 17 August 1993, col. 1-2, lines 42-8; col. 15, lines 1-2, 31-32, 43-44.	1,2,4,5,8,9
X,P	WO 98/19998 A2 (NOVARTIS AG) 14 May 1998, page 13, example 35.	1,2,5,10,19
X,P	WO 98/43964 A1 (PHARMACIA AND UPJOHN S.P.A) 08 October 1998, page 1, lines 4-28.	1,5,10,13, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
11 FEBRUARY 1999

Date of mailing of the international search report
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